

MEETING REVIEW

Neurogenesis in Cancun: where science meets the sea

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ABSTRACT

In March 2016, meeting organizers Sebastian Jessberger and Hongjun Song brought together over 100 scientists from around the world to Cancun, Mexico to present the latest research on neurogenesis. The meeting covered diverse aspects of embryonic and adult neurogenesis with a focus on novel technologies, including chemogenetics and optogenetics, live cell two-photon imaging, cell fate reprogramming and human pluripotent stem cell models. This Meeting Review describes the exciting work that was presented and some of the emerging themes from the meeting.

KEY WORDS: Adult neurogenesis, Hippocampus, Human pluripotent stem cell, Neural stem cell, Neurological disease, Subventricular zone

Introduction

The human brain is complex, with millions of neuronal subtypes and billions of connections. It is a specialized organ that controls how we learn and think, and the way we interact with other human beings. All of this complexity originates from a simple layer of neural stem cells in the embryo. Embryonic neural stem cells, also known as radial glial cells, divide and are specified into mature neuronal subtypes through a highly regulated process called neurogenesis. Embryonic neural stem cells become gradually quiescent, giving rise to adult neural stem cells in two distinct regions: the subventricular zone along the lateral ventricle and the subgranular zone in the dentate gyrus (DG). The 'Fusion Neurogenesis Conference: Implications for Lifelong Development and Disease' in Cancun, Mexico brought together scientists working on multiple aspects of neurogenesis to address fundamental principles of embryonic and adult neural stem cells and the adult-born neurons that are generated from them (Fig. 1). In this Meeting Review, we summarize new insights into the mechanisms that control neurogenesis and the functional implications of neurogenesis in normal physiological states and in the context of disease. In the first part of the review, we highlight the data presented on the basic molecular and cellular mechanisms of embryonic and adult neurogenesis. In the second part of the review, we focus on data regarding the functional implications of adult neurogenesis at the circuit and behavioral levels and the ability to target neurogenesis to promote repair and prevent disease. Finally, we summarise several presentations that described the use of human pluripotent stem cells (hPSCs) and differentiated neurons to create disease models in a dish, and provide food-for-thought on how far this field has come and where the hope lies for the future.

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Molecular and cellular mechanisms of neurogenesis

The keynote speaker, Magdalena Götz (Institute of Stem Cell Research, Helmholtz Center Munich and LMU, Germany) kicked off the meeting by reviewing basic concepts regarding how the number of adult neural stem cells/radial glia are determined in embryonic stages and how they become activated and depleted after injury or with age. Using live imaging in the adult zebrafish brain, she showed how radial glial cells can divide asymmetrically to generate a neuron, but most frequently directly differentiate into neurons without any division during the time in which they were imaged (Barbosa et al., 2015). After a stab wound injury, the pattern of radial glial cell division changes, with mostly symmetric divisions and migration down to the site of injury, which leads to a profound depletion of neural stem cells. Götz also presented two unpublished stories; one on the importance of the orientation of cell division for neural stem cell number, and another on the regulation of neural stem cell proliferation. In the first, Götz used a transgenic mouse model to show how the manipulation of *inscuteable*, a protein involved in spindle orientation, revealed a key role for vertical cell divisions in determining the number of adult neural stem cells of the subventricular zone during an early critical time window. In the second study, Götz discussed the role of the epithelium sodium channel (ENaC) in regulating the proliferation of adult neural stem cells. In the kidney, ENaCs respond to high shear stress. Similarly, in the brain, ENaCs may be sensing cerebrospinal fluid to control proliferation of adult subventricular neural stem cells: an interesting and provocative hypothesis.

The next set of talks by Sebastian Jessberger (University of Zurich, Switzerland), Michael Bonaguidi (University of Southern California, Los Angeles, USA), and Nicolas Toni (University of Lausanne, Switzerland) described the use of imaging techniques with fluorescent reporter mice to label and tease out the lineage hierarchy of adult neural stem cells at the population and clonal levels. One of the meeting's organizers, Jessberger showed direct evidence for the asymmetric and symmetric cell division of adult neural stem cells (also called type 1 or radial glial-like cells) by using time-lapse two-photon microscopy to image 1 mm into the CA1/dentate gyrus (DG) through a chronic cortical window. Bonaguidi extended previous work (Bonaguidi et al., 2011) using sparse labeling of adult neural stem cells in fixed tissue, wherein he described the existence of multipotent adult neural stem cells that self-renew through symmetric and asymmetric divisions, generating both neurons and astrocytes. He further talked about the identification of a new neural stem cell biased for neuron production. Toni described two distinct morphologies – termed a and b – of type 1 cells (Gebara et al., 2016) and speculated that type b cells might represent a transition between type a cells and astrocytes. Toni also presented ultrastructural data using electron microscopy of the type 1 radial glial-like cell, which will be a valuable resource in the field. Hongjun Song (Johns Hopkins University, Baltimore, USA), also one of the meeting organizers, rounded out the lineage-tracing talks with a new story on the clonal relationship of neural progenitors (using Gli1-CreERT2 and either

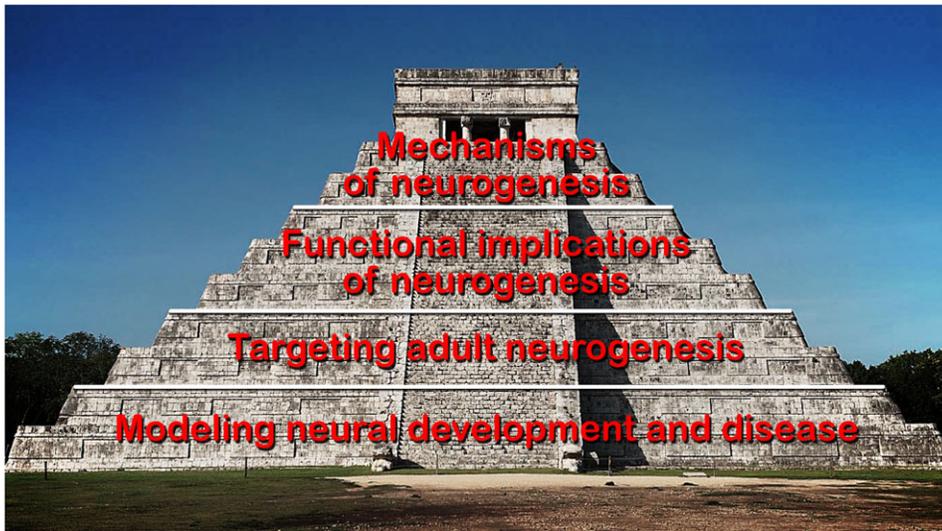


Fig. 1. An excursion to the ancient Mayan ruins of Chichen Itza provided the perfect opportunity to discuss the key themes of the meeting.

H2B-GFP or MADM11) in the thalamus, prethalamus and hypothalamus. This area of research has been somewhat understudied, as it has been difficult to perform lineage tracing because of the distinct spatial organization of the nuclear structures. With the help of computational tools to cluster clonal information, Song described a set of clonal principles with regards to the neural progenitor clones from these respective brain regions.

There were several talks on the molecular and cellular mechanisms that regulate adult neural stem cell self-renewal and the transition from quiescent stem cells to immature and mature neurons. Marlen Knobloch (University of Zurich, Switzerland) spoke about how fatty acid metabolism is linked to the quiescent state, which might be different than in other post-mitotic cells such as neurons and how manipulating the metabolic state can instruct neural stem cell behavior. Dieter Chichung Lie and Ruth Beckervordersandforth (Friedrich-Alexander University of Erlangen-Nuremberg, Germany) further elaborated on the importance of metabolic regulation in adult neurogenesis. They focused on the role of FoxO family transcription factors in autophagic flux regulation to promote dendritic development of newborn granule neurons and the role of mitochondrial metabolism in the transition of activated stem cells to intermediate precursor cells. Darcie Moore (University of Zurich, Switzerland) told a compelling story using fluorescent photobleaching and live cell imaging techniques of how neural stem cells segregate their ubiquitinated proteins through a diffusion barrier, which may be a possible mechanism to regulate stem cell aging (Moore et al., 2015).

Next, there were talks on transcriptome analysis, and chromatin- and microRNA-based mechanisms underlying neural stem cell fate. Xinyu Zhao (University of Wisconsin, Madison, USA) spoke about recently published work using a doublecortin-dsRed reporter to perform fluorescence-activated cell sorting (FACS) of newborn granule cells to understand the transcriptome heterogeneity at the single-cell level (Gao et al., 2016). Ana Martin-Villalba (German Cancer Research Center, Heidelberg, Germany) also described single-cell transcriptome analysis of subventricular zone neural stem cells after injury (Llorens-Bobadilla et al., 2015). Yukiko Gotoh (University of Tokyo, Japan) talked about epigenetic-based mechanisms in neural stem cells, specifically the role of the E3 ubiquitin ligase Ring1B, an essential component of the mammalian polycomb repressor complex (PRC1/2), in regulating H3K27me3 histone marks on neurogenic genes during embryonic cortical

development. Gotoh also spoke about the opposing role of HMGA, a family of high-mobility group proteins characterized by an AT-hook in this context (Hirabayashi et al., 2009) and described her elegant lineage-tracing studies, which uncovered the embryonic origin of adult subventricular zone neural stem cells (Furutachi et al., 2015). Alexey Terskikh (Sanford Burnham Prebys Medical Discovery Institute, San Diego, USA) continued with the theme of epigenetics, demonstrating how SOX2 binds bivalent or ‘poised’ chromatin, which is associated with both H3K4me3 and H3K27me3 marks, thus priming the epigenetic landscape in neural precursors and enabling coordinated gene activation and neuronal maturation during hippocampal neurogenesis (Amador-Arjona et al., 2015). Verdon Taylor (University of Basel, Switzerland) discussed his lab’s recent findings on the role of the microRNA processor Drosha and its regulation of a latent oligodendrocyte program in multipotent adult hippocampal neural stem cells. Together, these talks highlight the diversity of molecular and cellular approaches taken by various speakers and their labs in order to understand the detailed mechanisms that regulate adult neural stem cell self-renewal and fate choice.

Functional implications of adult neurogenesis at the circuit and behavioral levels

The next set of talks at the meeting focused on adult neurogenesis from the circuit and behavioral perspectives. Fred ‘Rusty’ Gage (Salk Institute, La Jolla, USA) talked about the use of an innovative FACS-based single-nuclei RNA sequencing technique to investigate the mechanisms of memory encoding. Using Prox1-EGFP⁺ reporter mice, Gage showed how a single-nuclei preparation of DG detects immediate early genes associated with a behavioral experience, whereas in whole-cell preparations of DG, the procedure itself may induce changes in immediate early genes, which warrants caution. Moreover, Gage’s transcriptional profiling data suggests that dentate granule cells exist in a continuum of states after exposure to a novel environment. Future studies are needed to understand the activity relationship between FOS⁺ and FOS[−] cells since, as suggested by Gage’s talk, the lack of FOS expression may not necessarily mean that neurons are inactive. Gage also presented data on the use of chronic imaging in the DG to visualize how newborn dentate granule cells undergo overgrowth and pruning during maturation stages. Surprisingly, even after exposure to an enriched environment, while there is faster dendritic development

there is greater pruning, suggesting the involvement of homeostatic mechanisms.

Alejandro Schinder (Fundacion Instituto Leloir, Argentina) spoke about the critical period of enhanced activity and synaptic plasticity of newborn granule cells and the stepwise innervation by excitatory and inhibitory inputs. He also presented recently published (Temprana et al., 2015) and unpublished data using optogenetics and chemogenetics to map the local target networks activated by adult-born neurons. Shaoyu Ge (Stonybrook University, New York, USA) continued the theme of circuit-level analysis by defining the mechanisms that control the initiation of circuit integration of adult-born neurons. He discussed how newborn dentate granule cells undergo an interesting pattern of 'leapfrog' migration whereby ontogenically related cells use gap junction coupling to migrate tangentially then radially into the granule cell layer.

The next few talks were focused on circuit mechanisms underlying the integration and encoding functions of adult-born neurons. Amar Sahay (Harvard Medical School, Boston, USA) presented evidence for how neuronal competition dictates integration of adult-born dentate granule cells in the hippocampus. He presented unpublished work showing how spine elimination in mature dentate granule cells drives integration of adult-born dentate granule cells. He leveraged this strategy to demonstrate a role for adult-born dentate granule cells in modulating global remapping in the dentate gyrus, a neural circuit mechanism that supports pattern separation. Rejuvenating the dentate gyrus with extra adult-born dentate granule cells reorganized local afferents and improved memory precision in adulthood, middle age and during aging. This idea was reiterated in Rene Hen's (Columbia University, New York, USA) talk where he presented recently published work on the proposed role of young granule cells in behavioral pattern separation (Danielson et al., 2016). Hen showed two-photon imaging of calcium ion transients using a viral-driven GCAMP6f construct in head-fixed mice to look at neuronal activity in young compared with mature granule cells. Interestingly, he found that while young granule cells are more active, they are less spatially tuned compared with mature granule cells. Upon a change in context, the level of global remapping of young granule cells is similar to mature granule cells, which Hen mentioned was a surprising result and the subject of ongoing analysis. Juan Song (University of North Carolina, Chapel Hill, USA) described the role of interneurons in the niche, in particular the role of cholecystokinin (CCK)-expressing interneurons and their regulation of quiescent neural stem cells. Using a chemogenetics approach to activate dentate CCK-expressing interneurons, Song found increased activation of quiescent neural stem cells, which is in sharp contrast to the role of parvalbumin-expressing interneurons in maintaining quiescence of neural stem cells (Song et al., 2013). Song's more recent data support the idea that multiple interneuron subtypes are involved in the complex circuit regulation of adult neural stem cells.

We also heard talks on the functional role of adult neurogenesis in learning and memory. Pierre-Marie Lledo (Institut Pasteur/CNRS, Paris, France) spoke about the role of adult subventricular zone neurogenesis in olfaction-related learning and memory. He provided information on the top-down control of adult-born neuron activity to encode hedonic values, as well as interesting new data on a possible connection between the microbiome and adult neurogenesis. Paul Frankland (Hospital for Sick Children, Toronto, Canada) talked about the role of hippocampal neurogenesis in forgetting and minimizing proactive interference

(Epp et al., 2016). In both Lledo's and Frankland's talks, optogenetic or chemogenetic approaches in awake mice were employed to corroborate and build upon previous findings with regard to the functional roles of adult-born neuron in learning and memory. Gerd Kempermann (Center for Regenerative Therapies, Dresden, Germany) shared recently published work (Garthe et al., 2016) that newborn neurons contribute to flexibility, in terms of water maze learning, in a stimulus-rich, cognitive-challenging environment. He also described fascinating ongoing studies in human subjects in virtual or land-based spatial navigation tasks that go some way towards translating the role of adult neurogenesis from mice to humans. Amelia Eisch (UT Southwestern Medical Center, Dallas, USA) described unpublished work on how entorhinal glutamatergic neuronal activity stimulates adult neurogenesis to mediate anti-depressive effects, providing a possible new target to prevent depression. Finally, Heather Cameron (National Institute of Mental Health, Bethesda, USA) emphasized in her talk that newborn neurons alter emotion-related behavior, even in tests that do not involve learning. Altogether, these talks underscore the idea that the identification of crucial cell types or niche components to modulate adult-born neurons may have therapeutic effects, such as the ability to prevent depressive-related behaviors or age-related cognitive deficits.

Targeting adult neurogenesis to promote repair and prevent disease

Neuron loss and disruption of the functional neural circuits are frequent consequences of traumatic injuries or neurodegeneration. Reprogramming the fate of endogenous reactive glial cells is emerging as a new approach for neuronal regeneration in the adult central nervous system. Chun-Li Zhang (UT Southwestern Medical Center, Dallas, USA) presented data on the molecular and cellular pathways regulating the *in vivo* reprogramming process in the adult brain and spinal cord. His group previously showed that ectopic expression of SOX2 is sufficient to convert resident reactive astrocytes into neuroblasts and mature neurons (Niu et al., 2013; Su et al., 2014). Through lineage tracing and genetic analyses in adult mice, Zhang's recent data revealed that SOX2-mediated *in vivo* reprogramming is a multistep cellular process: astrocytes are sequentially converted into ASCL1-expressing neural progenitors, DCX-expressing neuroblasts and then RBFOX3-positive neurons. This is an expandable process due to the proliferation of the converted progenitors and neuroblasts. Therefore, a single reprogrammed astrocyte can potentially generate multiple neurons. Both ASCL1 and the orphan nuclear receptor TLX are critically important for the reprogramming process (Islam et al., 2015; Niu et al., 2015). Interestingly, unpublished data further showed that SOX2-mediated *in vivo* reprogramming is governed by a cell cycle checkpoint. Removing this checkpoint can lead to a great increase of the number of reprogrammed neurons in the adult spinal cord. The theme of cell fate reprogramming was continued by Benedikt Berninger (University Medical Center, Mainz, Germany). His group previously showed that human pericytes can be converted into neuronal cells by the co-expression of SOX2 and ASCL1 under low-oxygen culture conditions (Karow et al., 2012). Of note, neither transcription factor alone was sufficient to induce cell fate change. In his talk, Berninger described how RNA-Seq analyses at two time points following induction of reprogramming revealed a synergistic action of these two factors in controlling global gene expression. These data suggest that, in contrast to the role of ASCL1 in mouse embryonic fibroblasts, ASCL1 does not act as a pioneer factor in adult human brain

pericytes. By contrast, SOX2 but not ASCL1 alone is capable of converting adult cortical NG2 glia into neurons (Heinrich et al., 2014). Interestingly, this SOX2-mediated *in vivo* reprogramming of cortical NG2 glia requires preconditioning induced by stab wound injury.

Cell transplantation holds therapeutic value for treating neurodegeneration and neurological diseases. Su-Chun Zhang (University of Wisconsin, Madison, USA) presented recent advances in neuronal differentiation of human pluripotent stem cells (hPSCs) and strategies for the regulation of human neural circuits after cell transplantation into adult animals. A different combination of developmental morphogens, such as retinoic acid, wingless (WNT), and sonic hedgehog (SHH), can guide hPSC-derived primitive neural stem cells to generate region-specific neurons in culture. Interestingly, after transplantation into the adult brain these pre-patterned neural progenitors have the intrinsic ability to differentiate into specific neuronal subtypes, which can mature and make long-distance axonal projections. For example, dopaminergic neuron progenitors transplanted into the brain of Parkinson's disease model mice differentiate into dopaminergic neurons and contribute to recovery of mouse motor deficits. Through a chemogenetics approach, the repaired neural circuit and its associated animal behavior can be modulated by a designer chemical (Chen et al., 2016).

Addition of new neurons in the adult brain may not always be beneficial. Seizure activity can induce robust generation of ectopically localized granule cells in the adult hippocampus. Jenny Hsieh (UT Southwestern Medical Center, Dallas, USA) showed that ablation of adult neurogenesis before pilocarpine-induced seizures in the nestin-TK transgenic mouse line can lead to improved cognitive function and a significant reduction of chronic seizure frequency (Cho et al., 2015). She further presented unpublished data using a chemogenetic approach to determine whether silencing adult-born neuronal activity can result in a reduction of seizure frequency. Interestingly, preliminary results showed that silencing seizure-induced neurons reduced their ectopic migration and changed the angle of primary dendrites. Jack Parent (University of Michigan, Ann Arbor, USA) summarized his group's research on epilepsy and aberrant hippocampal neurogenesis. Retrovirus-mediated tracing revealed abnormal sprouting of adult-born neurons after seizures. Electrophysiological recordings showed that ectopic adult-born neurons are most excitable, with increased firing frequency and amplitude. Conditional deletion of *Dab1*, a key component of the reelin signaling pathway, leads to ectopic migration of dentate granule cells. Although spontaneous seizures were not detected in mutant mice, they showed a reduced threshold to pilocarpine-induced status epilepticus (Korn et al., 2016). Kinichi Nakashima (Kyushu University, Japan) presented data showing how activated microglia can attenuate seizure-induced aberrant adult hippocampal neurogenesis. This beneficial effect of microglia requires DNA-activated TLR9 signaling through MYD88 and TNF- α (Matsuda et al., 2015). As such, TLR9 deletion increases recurrent seizure severity and exacerbates seizure-induced cognitive decline.

Exciting talks were also given on translational research. Mirjana Maletic-Savatic (Baylor College of Medicine, Houston, USA) described new improvements in magnetic resonance spectroscopy (MRS) as a method for measuring neurogenesis in the living human brain. A metabolic biomarker at the frequency of 1.28 ppm was previously shown to be enriched in neural progenitor cells (Manganas et al., 2007). An automated algorithm based on singular value decomposition was established

to scan 1.28 ppm peaks in individuals from multiple medical centers. This study revealed a strong association between this neurogenic biomarker and age, depression and antidepressant treatment in the live human brain. The biomarker also positively correlated with electroconvulsive therapy, which was previously shown to induce adult hippocampal neurogenesis in animal models. Therefore, the established biomarker might be a useful tool for understanding neurogenesis and human neurological diseases. Continuing with the theme of translational research, Ravi Jagasia (Roche, Basel, Switzerland) presented data on drug discovery and biomarker identification by using neural precursor cells (NPCs) derived from human embryonic stem cells. High-throughput and high-content screens identified compounds with the potent ability to promote neurogenesis in culture and animal models. One 'hit' compound showed beneficial effects on animal behaviors in several paradigms. In addition, proteomic profiling of NPCs identified glypican 2 as a potential biomarker for neurogenesis. It is present in human cerebral spinal fluid but greatly downregulated in an age-dependent manner.

Innovative strategies to model human neural development and neurological diseases

The development of hPSCs and human induced PSCs (hiPSCs) revolutionized research on human development and disease modeling. Rudolf Jaenisch (Whitehead Institute, Cambridge, USA) first raised critical issues on disease modeling in a dish, such as variations between cell lines and the complexity of cell-cell interactions. The use of isogenic cell lines and brain organoids in 3D culture might provide some solutions to these issues. He then presented recent data on interspecies chimeras (Cohen et al., 2016). Although at a much lower efficiency than corresponding rodent cells, human neural crest cells derived from hPSCs or hiPSCs can integrate and contribute to skin pigmentation in the host after injection into mouse embryos. Mouse-human chimeras such as these may provide a unique opportunity to study human tissue development and disease in live animals. Hongjun Song (Johns Hopkins University, Baltimore, USA) presented a second talk at the meeting, this time about the development of miniaturized spinning bioreactors via 3D printing. Brain organoids grown in these bioreactors showed uniform thickness of neuronal layers and marker expression. Furthermore, neuronal maturation and synapse formation were observed after extended incubation time. Song also presented exciting data on Zika virus. He showed how a particular strain of Zika virus can efficiently infect hiPSC-derived neural progenitors and release active virus particles (Tang et al., 2016) and how the infected cells exhibit increased cell death and are defective in cell cycle and gene expression. These data revealed an *in vitro* system for further studying Zika virus and for possible drug screening.

The next few talks focused on modeling human neurological diseases. Pierre Vanderhaeghen (University of Brussels, Belgium) discussed his work using 3D droplet cultures of hiPSCs to model human microcephaly primary hereditary (MCPH), which is caused by mutations in *ASPM*. A series of defects were observed, including precocious neuronal differentiation, mitotic spindle deviation, and abnormal induction of cortical progenitors. These defects could be mimicked by WNT overactivation and rescued by inhibition of the WNT signaling pathway. He then reported that after transplantation into neonatal mice, the hPSC-derived cortical cells maintain an intrinsic clock that requires a much longer time to become mature compared with their mouse counterparts, reminiscent of the *in vivo* situation. Importantly, human cortical cells can functionally



Fig. 2. Delegates of the FUSION Neurogenesis Conference in Cancun, Mexico.

integrate into local neural circuits after transplantation into lesioned adult mouse brains. Alysson Muotri (University of California, San Diego, USA) presented unpublished results focused on modeling the rare Aicardi-Goutieres syndrome (AGS) using hiPSCs from patients with *TREX1* mutations. The astrocytes from AGS-hiPSCs were found to be toxic, with increasing cytosolic single strand (ss) DNAs including LINE-1 elements, which further activated ssDNA-mediated innate immunity and resulted in the loss of co-cultured neurons through apoptosis. Interestingly, these defects could be rescued through inhibition of reverse transcriptase. By contrast, Silvia Cappello (Max Planck Institute of Psychiatry, Munich, Germany) spoke about modeling periventricular heterotopia using 3D organoid culture of hiPSCs. Mutations in either *FAT4* or *DCHS1* led to cortical heterotopia in cerebral organoids and multiple cellular defects in the organization of cytoskeleton and cilia. Finally, Sergiu Pasca (Stanford University, Stanford, USA) shared his group's research on using hPSCs to study human brain development and to model neuropsychiatric disorders. He described a novel 3D differentiating approach for generating a functional human cerebral cortex from hiPSCs, which contained pyramidal neurons of all layers and non-reactive astrocytes and which allows electrophysiological recordings in slices (Paşca et al., 2015). Pasca then shared his work on developing an iPSC-based model for studying neuronal phenotypes associated with 22q11.2 deletion syndrome – a common copy-number variant associated with psychosis and autism spectrum disorders. Together, these talks on the use of human pluripotent stem cells showed how these cells provide unique opportunities to understand human neural development and model diseases associated with the human nervous system.

Conclusions and perspectives

Unlocking the fundamental mechanisms and therapeutic potential of adult neurogenesis remains an important goal. It is clear from this meeting that various aspects – from basic principles to translational research – are beginning to be understood. With novel technologies and innovative strategies, one take-home message of the meeting is that we are making efficient progress towards translating *in vitro* to *in vivo* models and from animal models to human cells. Another theme of the meeting was a convergence of data addressing the functional aspects of newborn neurons in health and disease. The atmosphere and location of the meeting was relaxed and warm (Fig. 2). Undoubtedly influenced by the sapphire waters and white-sand beaches of Cancun, the speakers shared unpublished

work and had many stimulating discussions. Most, if not all, participants left the meeting with high hopes that we will continue to meet in the future to share progress in this rapidly evolving field.

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Competing interests

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